Background—The last few years have seen a considerable increase in the amount of information available concerning blood pressure (BP) and stroke associations. This article provides an overview of published reviews of the effects on stroke seen in trials of BP-lowering drugs and compares these with the results available from cohort studies.

Summary of Review—We present a review of major overviews of prospective cohort studies and an updated meta-analysis of >40 randomized controlled trials of BP lowering, which included >188,000 participants and approximately 6,800 stroke events. Cohort studies now indicate that in the Asia Pacific region as well as in North America and Western Europe, each 10 mm Hg lower systolic BP is associated with a decrease in risk of approximately one third in subjects aged 60 to 79 years. The association is continuous down to levels of at least 115/75 mm Hg and is consistent across sexes, regions, and stroke subtypes and for fatal and nonfatal events. The proportional association is age dependent but is still a strong and positive association in those aged 80 years. Data from randomized controlled trials, in which mean age at event was approximately 70 years, indicate that a 10 mm Hg reduction in systolic BP is associated with a reduction in risk of stroke of approximately one third. Per mm Hg systolic BP reduction, the benefits for stroke appear similar between agents, by baseline BP levels, and whether or not individuals have a past history of cardiovascular disease. There is, however, evidence of greater benefit with a larger BP reduction.

Conclusions—The epidemiologically expected benefits of BP lowering for stroke risk reduction are broadly consistent across a range of different population subgroups. There are greater benefits from larger BP reductions, and initiating and maintaining BP reduction for stroke prevention is a more important issue than choice of initial agent. (Stroke. 2004;35:776-785.)

Key Words: blood pressure ■ cohort studies ■ epidemiology ■ meta-analysis ■ randomized controlled trials ■ stroke

The risk of stroke increases continuously above blood pressure (BP) levels of approximately 115/75 mm Hg. Since the association is steep, and BP levels are high in most adult populations, almost two thirds of stroke burden globally is attributable to nonoptimal BP (ie, >115/75 mm Hg).1 Approximately two thirds of this burden occurs in middle-aged subjects (45 to 69 years), and approximately two thirds occurs in developing regions.

In 1990 it was demonstrated that in North American and Western European populations, a 5 mm Hg lower diastolic blood pressure (DBP) was associated with a 30% to 40% lower stroke risk,2 and this was reversed within a few years of BP lowering.3 Since then, further evidence has become available, especially in the elderly and in the Asia-Pacific region and from many more trials comparing different agents, more intensive and less intensive BP-lowering regimens, and BP lowering in those without hypertension. This article reviews published trial meta-analyses of the impact of pharmacological BP-lowering therapies on stroke across all population groups. The results are compared with overviews of cohort study data that assessed the association between BP and stroke in a range of populations. The main gaps in current research and the clinical and public health implications of the association of BP with stroke are also discussed.

Methods

Prospective Cohort Studies

Published overviews of cohort studies were identified by a search of MEDLINE and EMBASE databases with key words overview, meta-analysis, blood pressure, stroke or cerebrovascular or cardiovascular disease, cohort study or prospective study, and comparative study. Overviews were included if they were published or data were accessible by May 1, 2003, and if they provided data on inclusion criteria, number and regions of the cohort studies included, number of participants and demographics, duration of follow-up, disease end points, and methods of analyses. Results were independently extracted and summarized by 2 reviewers, but no additional analyses were conducted.

Randomized Controlled Trials

Meta-analyses of trials of BP-lowering agents were identified by a MEDLINE and EMBASE search with search terms overview,
by guest on April 15, 2017 http://stroke.ahajournals.org/ Downloaded from

meta-analysis, blood pressure or hypertension, stroke or cerebrovascular or cardiovascular disease, and randomized controlled trial. Data from individual trials included in these meta-analyses were included if they were published before May 1, 2003, and if they provided data on inclusion criteria, total number of participants and demographics, randomization method, trial interventions, trial end points, duration of follow-up, and net reduction in BP (ie, treatment effect). Data from individual studies, from both the trial and meta-analytic publications, were independently extracted by 2 reviewers. In some cases, existing meta-analyses of trials included the most recent data on individual trials, and therefore these were included in the final meta-analyses.

Core baseline and outcome data were extracted, and trials included in the meta-analysis were stratified into the following 3 subgroups to reduce clinical heterogeneity: (1) drug versus placebo or no treatment, (2) more intensive dose of drug versus less intensive dose of drug, and (3) drug versus drug. The net difference in BP between, for example, the treatment and placebo groups was calculated; this reflects the true difference in BP achieved as the influence of regression to the mean (which would be evident in both groups) is removed. The updated meta-analysis was based on summary data rather than individual participant data. The relative risk was computed as the measure of effect size for each trial and subgroup of trials. Statistical heterogeneity was assessed with the use of the standard Q statistic for heterogeneity, with a probability value of <0.1 used to indicate evidence of heterogeneity. A less stringent probability value of 0.1 was used because it is well known that tests of heterogeneity have low statistical power. If there was no evidence of statistical heterogeneity when this criterion was used, then the results were combined with the use of the standard inverse-variance weighted fixed effect approach.12 If there was evidence of statistical heterogeneity between the trials, attempts were made to explore potential sources of heterogeneity. If this was not possible, the random effects approach of DerSimonian and Laird13 was used as part of a sensitivity analysis to assess the robustness of the conclusions. When there were sufficient studies, evidence of publication bias was checked with the use of standard funnel plots.14

For each subgroup of trials, the weighted mean age, weighted mean follow-up, and weighted mean BP reduction were estimated. Trials were weighted by sample size and, in a sensitivity analysis, by number of stroke events.

Results

Prospective Cohort Studies

Five overviews of cohort studies assessing the association between BP and cardiovascular disease were identified. The

<table>
<thead>
<tr>
<th>TABLE 1. Major Overviews of Prospective Cohort Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Studies Collaboration (2002)</strong></td>
</tr>
<tr>
<td>No. of cohorts</td>
</tr>
<tr>
<td>Countries included</td>
</tr>
<tr>
<td>Inclusion criteria</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
</tr>
<tr>
<td>% male</td>
</tr>
<tr>
<td>Mean age (range) at baseline</td>
</tr>
<tr>
<td>Follow-up duration</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Stroke end points</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>RR with a 10-mm Hg decrease in SBP</td>
</tr>
<tr>
<td>Fatal versus nonfatal</td>
</tr>
<tr>
<td>Association by sex</td>
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<tr>
<td>Association by age</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Asia Pacific Cohort Studies Collaboration (2003)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cohorts</td>
</tr>
<tr>
<td>Countries included</td>
</tr>
<tr>
<td>Inclusion criteria</td>
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<td>No. of participants</td>
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<tr>
<td>% male</td>
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<tr>
<td>Mean age (range) at baseline</td>
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<tr>
<td>Follow-up duration</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Stroke end points</td>
</tr>
<tr>
<td>RR with a 10-mm Hg decrease in SBP</td>
</tr>
<tr>
<td>Fatal versus nonfatal</td>
</tr>
<tr>
<td>Association by sex</td>
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<tr>
<td>Association by age</td>
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<tr>
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</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; NR, not reported; RR, relative risk; CI, confidence interval.

MacMahon and Prospective Studies Collaboration (PSC) overviews included cohorts predominantly from the United Kingdom, United States, and Europe. Cohorts in the MacMahon and first PSC review were subsequently included in the later PSC review. The Eastern Stroke and Coronary Heart Disease Collaborative Research overview is a subset of the Asia Pacific Cohort Studies Collaboration (APCSC), which comprises cohorts from Mainland China, Hong Kong, Taiwan, Japan, Singapore, South Korea, Australia, and New Zealand. The PSC and APCSC overviews included almost 1 million and >420,000 individuals, respectively; both analyzed individual participant data and corrected for regression dilution bias to reflect true or “usual” BP levels. In total, 7 cohorts were included in the PSC and APCSC overviews, representing <5% and <10% of participants, respectively. The main characteristics and results of the overviews are summarized in Table 1.

An important finding in all overviews was that the association between BP and risk of stroke was continuous and log linear. Therefore, a given absolute difference in usual BP was associated with a similar relative risk reduction of stroke at all levels of BP. There was no evidence of a threshold below which levels of BP were no longer associated with lower relative risk of stroke, down to approximately 115 mm Hg systolic blood pressure (SBP) or 75 mm Hg DBP. All overviews commented on the statistical heterogeneity between studies, and age appeared to be an important factor, explaining approximately 80% of the between-study heterogeneity in APCSC. The strength of the overall association was not altered by restricting analyses to those with and without a history of coronary heart disease at baseline or by controlling for additional cardiovascular risk factors.

The overall risk estimates provided by APCSC, PSC, and previous meta-analyses (a 5 mm Hg lower DBP or 10 mm Hg lower SBP was associated with approximately a 30% to 40% lower risk of stroke) were influenced by the age of the cohorts, as the association of BP with stroke varied with age. The proportional change in stroke risk per unit change in BP was less extreme in old age than in middle age (Figure 1), but the relationship remained strong and positive for all age groups. Age attenuation limits the ability to directly compare the summary relative risk estimates across the overviews, but the 2 recent overviews that have published age-specific relative risks had similar results (Table 1); a 10 mm Hg lower SBP was associated with approximately a 40% to 50%, 30% to 40%, and 20% to 30% lower risk of stroke in those aged <60 years, 60 to 69 years, and ≥70 years, respectively. There has been no evidence in any of the overviews that the strength of association between BP and stroke varied by sex or for fatal and nonfatal stroke events. Regional comparisons in APCSC and PSC suggested that the association between BP and stroke in Asia was similar or even slightly steeper than in Australia and New Zealand, Europe, and the United States after standardization for age. In these 2 overviews the associations of BP with stroke subtypes were broadly similar, although low rates of CT/MRI confirmation would tend to obscure any differences.

Randomized Controlled Trials
Randomized controlled trials provide data on the impact of BP lowering on short-term stroke outcomes, which is relevant in assessing the extent to which the epidemiologically expected reductions in stroke are produced.

Randomized Controlled Trials Comparing Antihypertensive Drugs With a Placebo (or No Treatment)
Seventeen trials compared the effects of β-blocker and/or diuretic with a placebo or no treatment; in 6 trials the comparison drug was angiotensin-converting enzyme (ACE) inhibitors, and in 2 it was calcium antagonists (Table 2). In total, there were >73,500 participants and almost 2900 stroke events recorded in these trials. Weighted mean follow-up time for the 3 groups of trials ranged from 2 to 4.6 years, and the weighted mean age of participants ranged from 57 to 68 years. There was clear evidence of a reduction in stroke risk with BP lowering with each drug versus placebo comparison (P<0.005), with pooled relative risk reductions for β-blocker and/or diuretic, ACE inhibitors, and calcium antagonists of 35%, 28%, and 39%, respectively. These broadly similar relative risk reductions were achieved with weighted mean reductions in BP (SBP/DBP) of 13/6, 5/2, and 10/5 mm Hg, respectively. While the BP reductions appeared less for the ACE inhibitor versus placebo trials, there is also greater uncer-
There was no evidence of small study bias as assessed by a funnel plot (not shown) and no significant statistical heterogeneity in any of the 3 subgroup comparisons.

The trials comparing antihypertensive drugs with a placebo (or no treatment) were stratified by several trial characteristics such as mean age at entry, baseline BP, and history of cardiovascular disease (Figure 2). Overall, there was a reduction in risk of stroke of 30% and a risk reduction of approximately 30% to 40% in most subgroups. However, in several groups the risk reduction appeared to be greater with larger net reduction in BP, for example, in those with no past history of stroke/transient ischemic attack or vascular disease.

**Randomized Controlled Trials Comparing More Intensive Versus Less Intensive Antihypertensive Drug Regimens**

Three individually inconclusive clinical trials including a total of 20,408 participants and 384 stroke events compared treatment regimens of different intensities (Table 3). The

### TABLE 2. Randomized Controlled Trials Comparing Antihypertensive Drugs to a Placebo (or No Treatment)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Follow-Up, y</th>
<th>Mean Age, y</th>
<th>% Male</th>
<th>Net Difference*</th>
<th>SBP</th>
<th>DBP</th>
<th>RR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker and/or diuretic vs placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANBPS50</td>
<td>13</td>
<td>1721</td>
<td>22</td>
<td>1706</td>
<td>4</td>
<td>50</td>
<td>63</td>
<td>NR</td>
<td>6.09 (0.30–1.16)</td>
</tr>
<tr>
<td>Barraclough 51‡§</td>
<td>0</td>
<td>58</td>
<td>0</td>
<td>58</td>
<td>2</td>
<td>56</td>
<td>43</td>
<td>15</td>
<td>10.09 (0.0–49.56)</td>
</tr>
<tr>
<td>Carter et al62</td>
<td>10</td>
<td>49</td>
<td>21</td>
<td>48</td>
<td>4</td>
<td>NA</td>
<td>57</td>
<td>NR</td>
<td>57.04 (0.25–0.88)</td>
</tr>
<tr>
<td>Coope13</td>
<td>20</td>
<td>419</td>
<td>39</td>
<td>465</td>
<td>4.4</td>
<td>69</td>
<td>31</td>
<td>18</td>
<td>11.07 (0.34–0.96)</td>
</tr>
<tr>
<td>Dutch TIA14</td>
<td>52</td>
<td>732</td>
<td>62</td>
<td>741</td>
<td>2.6</td>
<td>65</td>
<td>64</td>
<td>8</td>
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<tr>
<td>EWPHE55</td>
<td>32</td>
<td>416</td>
<td>48</td>
<td>424</td>
<td>4.7</td>
<td>72</td>
<td>30</td>
<td>21</td>
<td>8.06 (0.44–1.04)</td>
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<tr>
<td>HDFP56–60</td>
<td>102</td>
<td>5485</td>
<td>158</td>
<td>5455</td>
<td>5</td>
<td>51</td>
<td>55</td>
<td>NR</td>
<td>5.06 (0.50–0.82)</td>
</tr>
<tr>
<td>HSUG I II III12</td>
<td>43</td>
<td>233</td>
<td>52</td>
<td>219</td>
<td>2.3</td>
<td>59</td>
<td>41</td>
<td>25</td>
<td>12.08 (0.54–1.11)</td>
</tr>
<tr>
<td>MRC older62</td>
<td>101</td>
<td>2183</td>
<td>134</td>
<td>2213</td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>14</td>
<td>7.06 (0.59–0.98)</td>
</tr>
<tr>
<td>MRC young63</td>
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<td>8700</td>
<td>109</td>
<td>8654</td>
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<td>52</td>
<td>52</td>
<td>11</td>
<td>6.05 (0.40–0.75)</td>
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<tr>
<td>Oslo64,65</td>
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<td>406</td>
<td>5</td>
<td>379</td>
<td>5.5</td>
<td>45</td>
<td>100</td>
<td>17</td>
<td>10.08 (0.00–1.53)</td>
</tr>
<tr>
<td>SHEP66‡</td>
<td>105</td>
<td>2365</td>
<td>162</td>
<td>2371</td>
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<td>72</td>
<td>43</td>
<td>12</td>
<td>4.06 (0.51–0.83)</td>
</tr>
<tr>
<td>STOP H67</td>
<td>30</td>
<td>812</td>
<td>55</td>
<td>815</td>
<td>2.1</td>
<td>76</td>
<td>37</td>
<td>20</td>
<td>8.05 (0.35–0.85)</td>
</tr>
<tr>
<td>USPHS68‡</td>
<td>1</td>
<td>193</td>
<td>6</td>
<td>196</td>
<td>7</td>
<td>44</td>
<td>80</td>
<td>15</td>
<td>10.07 (0.02–1.39)</td>
</tr>
<tr>
<td>Woff et al73</td>
<td>2</td>
<td>45</td>
<td>1</td>
<td>42</td>
<td>1.4</td>
<td>49</td>
<td>32</td>
<td>NR</td>
<td>20.17 (0.18–19.8)</td>
</tr>
</tbody>
</table>

Summary †

![Table continued](http://stroke.ahajournals.org/)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Follow-Up, y</th>
<th>Mean Age, y</th>
<th>% Male</th>
<th>Net Difference*</th>
<th>SBP</th>
<th>DBP</th>
<th>RR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors vs placebo</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>HOPE74</td>
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<td>4654</td>
<td>226</td>
<td>4652</td>
<td>5</td>
<td>66</td>
<td>73</td>
<td>3</td>
<td>1.06 (0.57–0.84)</td>
</tr>
<tr>
<td>PART 275</td>
<td>7</td>
<td>308</td>
<td>4</td>
<td>309</td>
<td>4</td>
<td>61</td>
<td>82</td>
<td>6</td>
<td>4.17 (0.52–5.94)</td>
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<tr>
<td>PROGRESS27</td>
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<td>3051</td>
<td>420</td>
<td>3054</td>
<td>4</td>
<td>64</td>
<td>70</td>
<td>9</td>
<td>4.03 (0.64–0.84)</td>
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<tr>
<td>QUIET18</td>
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<td>878</td>
<td>1</td>
<td>872</td>
<td>2</td>
<td>58</td>
<td>82</td>
<td>NR</td>
<td>NR 9.99 (0.06–15.8)</td>
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<td>SCAT72‡</td>
<td>2</td>
<td>229</td>
<td>9</td>
<td>231</td>
<td>5</td>
<td>61</td>
<td>89</td>
<td>4</td>
<td>3.02 (0.05–1.03)</td>
</tr>
<tr>
<td>TEST73</td>
<td>3</td>
<td>372</td>
<td>69</td>
<td>348</td>
<td>2.6</td>
<td>70</td>
<td>60</td>
<td>4</td>
<td>3.10 (0.75–1.35)</td>
</tr>
</tbody>
</table>

Summary †

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Follow-Up, y</th>
<th>Mean Age, y</th>
<th>% Male</th>
<th>Net Difference*</th>
<th>SBP</th>
<th>DBP</th>
<th>RR and 95% CI</th>
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<tr>
<td>Calcium antagonists vs placebo</td>
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<td>408</td>
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<td>57</td>
<td>80</td>
<td>5</td>
<td>4.09 (0.29–3.35)</td>
</tr>
<tr>
<td>Syd-Eur47</td>
<td>47</td>
<td>2398</td>
<td>77</td>
<td>2297</td>
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<td>70</td>
<td>33</td>
<td>11</td>
<td>5.08 (0.41–0.84)</td>
</tr>
<tr>
<td>Summary †</td>
<td>52</td>
<td>2815</td>
<td>82</td>
<td>2705</td>
<td>2</td>
<td>68</td>
<td>40</td>
<td>10</td>
<td>5.01 (0.44–0.85)</td>
</tr>
</tbody>
</table>

n = number of events; N = number of participants. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; RR, relative risk; 95% CI, 95% confidence interval; NR, not recorded.

*Net BP difference = blood pressure difference between the randomized groups in mm Hg (ie, BP change in treatment group − BP change in placebo group).

†Summary follow-up, mean age, % male, and net SBP and DBP change are weighted by study size for those studies that provided data on net changes in both SBP and DBP. Weighting by number of events made negligible difference. The pooled RR and 95% CI (using the fixed effects approach) for each of the 3 trial subgroups are presented, and the test for heterogeneity (Q statistic and P value) are Q = 14.23, P = 0.36; Q = 8.90, P = 0.11; and Q = 0.61, P = 0.43, respectively.

‡These trials also included older classes of drugs such as methyldopa and alkaloids.

§There were no stroke events in the Barraclough or VA-NHLBI trial; however, for the purposes of meta-analyses, 0.5 was added to all cells in the 2×2 table.

tertainty over the BP reductions in this subgroup. There was no evidence of small study bias as assessed by a funnel plot (not shown) and no significant statistical heterogeneity in any of the 3 subgroup comparisons.

The trials comparing antihypertensive drugs with a placebo (or no treatment) were stratified by several trial characteristics such as mean age at entry, baseline BP, and history of cardiovascular disease (Figure 2). Overall, there was a reduction in risk of stroke of 30% and a risk reduction of approximately 30% to 40% in most subgroups. However, in several groups the risk reduction appeared to be greater with larger net reduction in BP, for example, in those with no past history of stroke/transient ischemic attack or vascular disease.
TABLE 3. Randomized Controlled Trials Comparing More Intensive vs Less Intensive Antihypertensive Drug Regimens

<table>
<thead>
<tr>
<th>Blood pressure lowering trials</th>
<th>Net difference in SBP/DBP</th>
<th>Relative risk reduction of stroke (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>12/4</td>
<td>40% (26–57%)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>6/3</td>
<td>28% (23–35%)</td>
</tr>
<tr>
<td>75+ years</td>
<td>15/6</td>
<td>28% (21–35%)</td>
</tr>
<tr>
<td>Mean baseline SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 140 mmHg</td>
<td>3/1</td>
<td>30% (15–45%)</td>
</tr>
<tr>
<td>140–160 mmHg</td>
<td>10/4</td>
<td>20% (17–34%)</td>
</tr>
<tr>
<td>&gt; 160 mmHg</td>
<td>15/6</td>
<td>32% (25–38%)</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few/no participants</td>
<td>11/5</td>
<td>10% (28–41%)</td>
</tr>
<tr>
<td>Mortal participants</td>
<td>9/4</td>
<td>22% (12–31%)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few/no participants</td>
<td>13/6</td>
<td>35% (39–45%)</td>
</tr>
<tr>
<td>Mortal participants</td>
<td>6/3</td>
<td>24% (16–31%)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>30% (26–32%)</td>
</tr>
</tbody>
</table>

Figure 2. Randomized controlled trials comparing antihypertensive drugs with a placebo (or no treatment) by subgroup. The meta-analyses of BP-lowering trials are presented stratified into subgroups on the basis of mean age of trial participants at entry, baseline SBP level, and whether trial participants predominantly had a history of stroke/transient ischemic attack (TIA) or vascular disease. The diamonds are centered on the pooled estimate of effect and represent 95% CI. The solid diamond represents the pooled relative risk and 95% CI for all contributing trials.

meta-analysis suggested that additional benefit may be gained from a more intensive treatment regimen (relative risk reduction of 20%; P=0.04). There was no significant statistical heterogeneity.

Randomized Controlled Trials Comparing Different Antihypertensive Drugs
Fifteen trials compared the effects of different types of antihypertensive drugs, with 2 trials including several drug versus drug comparisons (Table 4).80–92 In total, there were >96 000 participants and almost 3600 stroke events recorded over a mean follow-up time of 4 to 5 years. The weighted mean reduction in BP in many of the drug versus drug trials was small, often <1 mm Hg SBP and DBP (Table 4). Overall, these trials indicated that there was little difference between the drug classes, with relative risk reductions of 9% (β-blockers and/or diuretics versus ACE inhibitors), −8% (β-blockers and/or diuretics versus calcium antagonists), and 11% (calcium antagonists versus ACE inhibitors). These results were of borderline statistical significance. The latter subgroup was the only one in which there was evidence of statistical heterogeneity (P=0.09), and a random effects model gave a nonsignificant relative risk reduction of 5%.

Net Reduction in BP and Relative Risk Reduction in Stroke
A meta-regression analysis was used to assess the direct relationship between the net reduction in SBP in the 7 trial meta-analyses. The net reduction in SBP was plotted against the relative risk reduction in stroke for each meta-analysis. This plot suggested that a dose-response relationship may exist (Figure 3). A weighted linear regression line was superimposed in which weights are equal to the inverse of the variance for each trial meta-analysis. The slope of this weighted regression line indicated that a 10 mm Hg greater reduction in SBP would be associated with a reduction in risk of stroke of 31% (R=0.71). The mean weight circle duration for all these trials was 4.5 years, and the mean age of participants at entry into trials was 63 years (the mean age at event is likely to be approximately a decade later). Age-specific analyses from the 2 cohort study overviews16,18 estimated that a 10 mm Hg lower SBP in participants aged 60 to 69 years at event was associated with a risk reduction in stroke of approximately 35%; for those aged ≥70 years the risk reduction was 25% to 29% (Table 5). The results from cohort studies and randomized controlled trials are therefore broadly consistent, suggesting that most of the “epidemiologically expected” benefit of BP lowering is achieved within a few years for stroke.

Discussion
Cohort studies have demonstrated that the strong association between BP and stroke appears to be continuous down to levels of at least 115/75 mm Hg. The strength of the association was similar for men and women and for fatal and nonfatal events but attenuated with age.2,15–18 Despite a potentially weaker relative association for older age groups, the higher overall stroke rate in this group means that in absolute terms, the benefits of a given reduction in BP are likely to be greater. The analyses have not consistently demonstrated a difference in the association between intracerebral hemorrhage and ischemic stroke; however, only approximately one half of stroke subtypes were confirmed (CT, MRI, or autopsy). Regional comparisons are very limited.
because most of the cohort studies have been conducted primarily in the “developed” parts of the world; however, the broad consistency of the results across surveys was more evident than any differences. This suggests that the proportional associations are likely to be reasonably generalizable to the many populations in the world (eg, Africa, South America) for which there are limited data on stroke epidemiology.25

Data from trials provide more reliable data on the likely short-term benefits of BP lowering on stroke. As with the cohort data, randomized controlled trials have been conducted predominantly in populations of Western countries, and data for developing countries (where approximately three quarters of stroke deaths occur worldwide26) are very scarce. The results of the updated meta-analysis of trials are consistent with those of several previous meta-analyses and confirmed the risk reduction of stroke with BP lowering compared with placebo (regardless of the agent used) as being between 30% and 40%. Previous analyses have also found no evidence of a difference in effect size for men and women or for fatal and nonfatal events.3–8

Limited data were available on treatment effects by age, and the treatment effects by age within individual trials27 and between trials3,5,9,10,28 have not been consistent. However, the trials were often not powered for age subgroup analyses and often included only a narrow age band. Few data are available on stroke subtypes, limiting the scope for meta-analyses. The limited data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)27 and the Heart Outcome Prevention Evaluation (HOPE) study29 are insufficient to draw conclusions regarding the impact of BP lowering on stroke subtypes. Analyses have indicated, however, that a more intensive BP-lowering regimen with a given agent may produce a greater risk reduction than a...
Heart Attack Trial (ALLHAT)\textsuperscript{30} and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE)\textsuperscript{31,32} were not included in the meta-analysis because no other trials included the same classes of drugs. They indicated that there was a higher risk of stroke in the \(\alpha\)-adrenergic blocker group compared with diuretics\textsuperscript{30} and that angiotensin II blockers may have greater impact on stroke than \(\beta\)-blockers.\textsuperscript{31,32}

### Shape and Size of Association Between BP and Stroke

There has been considerable debate over the shape of the association between BP and stroke. The data presented here from cohort studies suggested a continuous log-linear association. However, some other cohort data appear to have demonstrated a J-shaped curve,\textsuperscript{33–37} and it has been suggested that this relationship indicates that BP has been lowered too far and that cerebral blood flow is compromised, leading to ischemia. It is more likely to reflect deteriorating health, which accounts for both falling pressure and a greater likelihood of a cardiovascular disease event, but the 2 factors may not be causally related.\textsuperscript{38–43} Several trials have found no evidence of a J-curve association despite including subgroups of patients susceptible to reduced perfusion.\textsuperscript{44–47} The large PROGRESS\textsuperscript{48} and HOPE\textsuperscript{29} trials found no evidence of a J-curve association across a wide range of BP levels. Overall, these results support a log-linear association and indicate that a potential J-curve relationship should not detract attention from the major benefits of BP lowering.

A key finding from this article is that the 7 meta-analyses of randomized controlled trials of BP lowering and stroke suggest a dose-response relationship. At mean age at baseline of approximately 63 years, a 10 mm Hg reduction in SBP was associated with a risk reduction in stroke of 31%. Given that most of these individuals would not have experienced their stroke event until approximately a decade later, the results are consistent with the predicted reduction in stroke risk from the cohort study data. This indicates that most of the epidemiologically expected benefit of BP lowering may be achieved within a few years for stroke.

### Future Research and Implications for Prevention

Research and analyses from cohort study collaborations such as APCSC and meta-analysis of individual participant trial

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**Figure 3.** Net reduction in SBP and relative risk reduction in stroke in randomized controlled trials of BP lowering. In a meta-regression, the direct relationship between the net reduction in SBP was plotted against the relative risk reduction in stroke for each of the 7 trial meta-analyses. The slope of the weighted linear regression line (where weights are equal to the inverse of the variance for each trial meta-analysis) indicated that a 10 mm Hg greater reduction in SBP would be associated with a reduction in risk of stroke of 31% (\(R^2=0.71\)). From left to right, the diamonds represent the meta-analyses for \(\beta\)-blockers and/or diuretics vs calcium antagonists, calcium antagonists vs ACE inhibitors, and \(\beta\)-blockers and/or diuretics vs ACE inhibitors; the circle represents the more intensive vs less intensive antihypertensive drug regimens; and the squares are ACE inhibitors vs placebo, calcium antagonists vs placebo, and \(\beta\)-blockers and/or diuretics vs placebo or no treatment. The sizes of the diamonds, circle, and squares are larger where there are more events because their size is proportional to the inverse variance of that comparison; vertical lines represent 95% CI.

---

**Table 5.** Relative Risk Reduction in Stroke With a Reduction in Systolic Blood Pressure Predicted From Cohort Studies and Observed From Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Predicted Effects on Stroke of Lowering SBP 10 mm Hg*</th>
<th>Observed Effects on Stroke With a Reduction in SBP of 10 mm Hg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age at Event</td>
<td>Estimated Mean Age at Event</td>
</tr>
<tr>
<td>60–69 Years</td>
<td>Approximately 73 Years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk Reduction</th>
<th>Estimated SBP Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective Studies Collaboration (2002)\textsuperscript{16}</td>
<td>34%</td>
<td>31%</td>
</tr>
<tr>
<td>Asia Pacific Cohort Studies Collaboration (2003)\textsuperscript{18}</td>
<td>36%</td>
<td>25%</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure.

*Relative risk reduction in stroke from cohort studies with a 10-mm Hg lower SBP, by age at event.
†Relative risk reduction in stroke from randomized controlled trials with a 10-mm Hg reduction in SBP based on the slope of the regression line in Figure 3. Mean age at entry into trials was 63 years, and mean age at event is likely to approximately a decade later, ie, 73 years.
data improve the understanding of the associations between BP and stroke and the potential benefits of BP lowering in different population subgroups. Additional analyses are able to examine the combined impact of multiple risk factors on stroke risk. BP intervention strategies would be greatly enhanced if these data were also used in the improvement of risk prediction frameworks to better identify those at higher absolute risk of cardiovascular disease. Development of simple versions of these risk prediction tools would be of particular value in developing regions where much of the future cardiovascular disease burden is likely to occur.

Future trial analyses should focus on the presence or absence of age attenuation in the effect of BP lowering. This would require comparison of age-specific, follow-up time-specific, and end point–specific analyses of individual participant data from both observational studies (such as APCSC) and clinical trials (such as the Blood Pressure Lowering Treatment Trialists’ Collaboration11). Given that most individuals require combination therapy, it is also important to shift the focus of trials from comparisons of the short-term benefits of individual drugs. Instead, future trials should aim to determine the optimal combination therapy and the potential long-term benefits of different antihypertensive regimens in different population subgroups. While there may be some differences between BP-lowering agents, the relative differences between these agents are minor compared with the relative benefits of any BP-lowering agent versus no treatment.

Finally, it is important to acknowledge that treatment of high-risk groups will only partially address the growing cardiovascular disease epidemic. Data presented in this article indicated that the relative benefits of BP lowering are not only limited to those classified as hypertensive but would also be evident in those with normal or below normal BP. These relative benefits appear broadly consistent across many population subgroups. Other important areas of research therefore include exploration of cost-effective strategies to bring about population changes in cardiovascular risk factors such as BP. Such initiatives would complement targeted treatment approaches and would not only benefit the developed world but could potentially arrest the projected increase in cardiovascular disease in developing countries.

Acknowledgments
This study was supported by a Health Research Council (New Zealand) fellowship to Dr Lawes. Dr Rodgers is a National Health Foundation (New Zealand) Senior Research Fellow. We thank Varsha Parag and Ruey-Bin Lin for statistical assistance and Clarissa Could-Thorpe for secretarial support.

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results of the Controlled Onset Verapamil Investigation of Cardiovascular Events (CONVINCE) trial. JAMA. 2003;289:1510–1516.


Blood Pressure and Stroke: An Overview of Published Reviews
Carlene M.M. Lawes, Derrick A. Bennett, Valery L. Feigin and Anthony Rodgers

Stroke. 2004;35:776-785; originally published online February 19, 2004;
doi: 10.1161/01.STR.0000116869.64771.5A
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/35/3/776

An erratum has been published regarding this article. Please see the attached page for:
/content/35/4/1024.full.pdf
The article entitled “Blood Pressure and Stroke: An Overview of Published Reviews,” by Lawes et al\(^1\) contained incorrect data resulting from a production error. The corrected article appears below. The publisher regrets the error.

**Blood Pressure and Stroke**  
**An Overview of Published Reviews**

Carlene M.M. Lawes, MBChB, FAFPHM, PhD; Derrick A. Bennett, MSc, PhD, CStat; Valery L. Feigin, MD, MSc, PhD; Anthony Rodgers, MBChB, FAFPHM, PhD

**Background**—The last few years have seen a considerable increase in the amount of information available concerning blood pressure (BP) and stroke associations. This article provides an overview of published reviews of the effects on stroke seen in trials of BP-lowering drugs and compares these with the results available from cohort studies.

**Summary of Review**—We present a review of major overviews of prospective cohort studies and an updated meta-analysis of \(>40\) randomized controlled trials of BP lowering, which included \(>\text{188 000}\) participants and approximately \(6800\) stroke events. Cohort studies now indicate that in the Asia Pacific region as well as in North America and Western Europe, each \(10\) mm Hg lower systolic BP is associated with a decrease in risk of stroke of approximately one third in subjects aged 60 to 79 years. The association is continuous down to levels of at least \(115/75\) mm Hg and is consistent across sexes, regions, and stroke subtypes and for fatal and nonfatal events. The proportional association is age dependent but is still strong and positive in those aged 80 years. Data from randomized controlled trials, in which mean age at event was approximately 70 years, indicate that a \(10\) mm Hg reduction in systolic BP is associated with a reduction in risk of stroke of approximately one third. Per mm Hg systolic BP reduction, the relative benefits for stroke appear similar between agents, by baseline BP levels, and whether or not individuals have a past history of cardiovascular disease. There is, however, evidence of greater benefit with a larger BP reduction.

**Conclusions**—The epidemiologically expected benefits of BP lowering for stroke risk reduction are broadly consistent across a range of different population subgroups. There are greater benefits from larger BP reductions, and initiating and maintaining BP reduction for stroke prevention is a more important issue than choice of initial agent. *(Stroke. 2004;35:1024-1033.)*

**Key Words:** blood pressure ■ cohort studies ■ epidemiology ■ meta-analysis ■ randomized controlled trials ■ stroke

The risk of stroke increases continuously above blood pressure (BP) levels of approximately \(115/75\) mm Hg. Since the association is steep, and BP levels are high in most adult populations, almost two thirds of stroke burden globally is attributable to nonoptimal BP (ie, \(>115/75\) mm Hg).\(^1\) Approximately two thirds of this burden occurs in middle-aged subjects (45 to 69 years), and approximately two thirds occurs in developing regions.

In 1990 it was demonstrated that in North American and Western European populations, a \(5\) mm Hg lower diastolic blood pressure (DBP) was associated with a 30\% to 40\% lower stroke risk,\(^2\) and this was reversed within a few years of BP lowering.\(^3\) Since then, further evidence has become available, especially in the elderly and in the Asia-Pacific region and from many more trials comparing different agents, more intensive and less intensive BP-lowering regimens, and BP lowering in those without hypertension. This article reviews published trial meta-analyses of the impact of pharmacological BP-lowering therapies on stroke across all population groups. The results are compared with overviews of cohort study data that assessed the association between BP and stroke in a range of populations. The main gaps in current research and the clinical and public health implications of the association of BP with stroke are also discussed.
Methods

Prospective Cohort Studies
Published overviews of cohort studies were identified by a search of MEDLINE and EMBASE databases with key words overview, meta-analysis, blood pressure, stroke or cerebrovascular or cardiovascular disease, cohort study or prospective study, and comparative study. Overviews were included if they were published or data were accessible by May 1, 2003, and if they provided data on inclusion criteria, number and regions of the cohort studies included, number of participants and demographics, duration of follow-up, disease endpoints, and methods of analyses. Results were independently extracted and summarized by 2 reviewers, but no additional analyses were conducted.

Randomized Controlled Trials
Meta-analyses of trials of BP-lowering agents were identified by a MEDLINE and EMBASE search with search terms overview, meta-analysis, blood pressure or hypertension, stroke or cerebrovascular or cardiovascular disease, and randomized controlled trial. Data from individual trials included in these meta-analyses were included if they were published before May 1, 2003, and if they provided data on inclusion criteria, total number of participants and demographics, randomization method, trial interventions, trial end points, duration of follow-up, and net reduction in BP (ie, treatment effect). Data from individual studies, from both the trial and meta-analytic publications, were independently extracted by 2 reviewers. In some cases, existing meta-analyses of trials included the most recent data on individual trials, and therefore these were included in the final meta-analyses.

Core baseline and outcome data were extracted, and trials included in the meta-analysis were stratified into the following 3 subgroups to reduce clinical heterogeneity: (1) drug versus placebo or no treatment, (2) more intensive dose of drug versus less intensive dose of drug, and (3) drug versus drug. The net difference in BP between, for example, the treatment and placebo groups was calculated; this reflects the true difference in BP achieved as the influence of regression to the mean (which would be evident in both groups) is removed. The updated meta-analysis was based on summary data rather than individual participant data. The relative risk was computed as the measure of effect size for each trial and subgroup of trials. Statistical heterogeneity was assessed with the use of the standard Q statistic for heterogeneity, with a probability value of <0.1 used to indicate evidence of heterogeneity. A less stringent probability value of 0.1 was used because it is well known that tests of heterogeneity have low statistical power. If there was no evidence of statistical heterogeneity when this criterion was used, then the results were combined with the use of the standard inverse-variance weighted fixed effect approach. If there was evidence of statistical heterogeneity between the trials, attempts were made to explore

### TABLE 1. Major Overviews of Prospective Cohort Studies

<table>
<thead>
<tr>
<th>No. of cohorts</th>
<th>61</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries included</td>
<td>Europe, United States, Asia, Australia</td>
<td>Mainland China, Japan, Hong Kong, Taiwan, Singapore, South Korea, New Zealand, Australia</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>• At least 5000 person-years of follow-up recorded or planned</td>
<td>• Population from the Asia Pacific region</td>
</tr>
<tr>
<td></td>
<td>• Date of birth or age, sex, blood pressure, and cholesterol recorded at baseline</td>
<td>• At least 5000 person-years of follow-up recorded or planned</td>
</tr>
<tr>
<td></td>
<td>• Date of death or age at death recorded during follow-up</td>
<td>• Date of birth or age, sex, and blood pressure recorded at baseline</td>
</tr>
<tr>
<td>No. of participants</td>
<td>958,074</td>
<td>425,325</td>
</tr>
<tr>
<td>% male</td>
<td>NR</td>
<td>57% (range 34%-100%)</td>
</tr>
<tr>
<td>Mean age (range) at baseline</td>
<td>NR</td>
<td>47 (20–107) years</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Range 4–17 years</td>
<td>Range 2–27 years</td>
</tr>
<tr>
<td></td>
<td>Mean 12 years</td>
<td>Mean 7 years</td>
</tr>
<tr>
<td></td>
<td>12.7 million person years</td>
<td>3.0 million person years</td>
</tr>
<tr>
<td>Stroke end points</td>
<td>11,960 strokes</td>
<td>5178 strokes</td>
</tr>
<tr>
<td></td>
<td>100% fatal</td>
<td>50% fatal</td>
</tr>
<tr>
<td>RR with a 10-mm Hg decrease in SBP</td>
<td>NR</td>
<td>0.63 (95% CI 0.61–0.64)</td>
</tr>
<tr>
<td></td>
<td>(37% decrease in stroke risk)</td>
<td></td>
</tr>
<tr>
<td>Fatal versus nonfatal</td>
<td>No significant difference</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Association by sex</td>
<td>No significant difference &gt;60 years of age</td>
<td></td>
</tr>
<tr>
<td>Association by age</td>
<td>For a 10-mm Hg lower SBP</td>
<td>For a 10-mm Hg lower SBP</td>
</tr>
<tr>
<td>40–49 years RR</td>
<td>0.60 (0.57–0.63)</td>
<td>&lt;60 years RR</td>
</tr>
<tr>
<td>50–59 years RR</td>
<td>0.62 (0.59–0.63)</td>
<td>60–69 years RR</td>
</tr>
<tr>
<td>60–69 years RR</td>
<td>0.66 (0.64–0.67)</td>
<td>≥ 70 years RR</td>
</tr>
<tr>
<td>70–79 years RR</td>
<td>0.71 (0.69–0.72)</td>
<td></td>
</tr>
<tr>
<td>80–89 years RR</td>
<td>0.82 (0.79–0.84)</td>
<td></td>
</tr>
</tbody>
</table>

Five overviews of cohort studies assessing the association between BP and cardiovascular disease were identified. The MacMahon and Prospective Studies Collaboration (PSC)15,16 overviews included cohorts predominantly from the United Kingdom, United States, and Europe. Cohorts in the MacMahon2 and first PSC review were subsequently included in the later PSC review.16 The Eastern Stroke and Coronary Heart Disease Collaborative Research overview is a subset of the Asia Pacific Cohort Studies Collaboration (APCSC),18 which comprises cohorts from mainland China, Hong Kong, Taiwan, Japan, Singapore, South Korea, Australia, and New Zealand. The PSC and APCSC overviews included almost 1 million and >420,000 individuals, respectively; both analyzed individual participant data and corrected for regression dilution bias to reflect true or “usual” BP levels.16 In total, 7 cohorts were included in both the PSC and APCSC overviews, representing <5% and <10% of participants, respectively. The main characteristics and results of the overviews are summarized in Table 1.

An important finding in all overviews was that the association between BP and stroke was continuous and log linear. Therefore, a given absolute difference in usual BP was associated with a similar relative risk reduction of stroke at all levels of BP. There was no evidence of a threshold below which levels of BP were no longer associated with lower relative risk of stroke, down to approximately 115 mm Hg systolic blood pressure (SBP) or 75 mm Hg DBP.16,18 All overviews commented on the statistical heterogeneity between studies, and age appeared to be an important factor,16,18 explaining approximately 80% of the between-study heterogeneity in APCSC.18 The strength of the overall association was not altered by restricting analyses to those with and without a history of coronary heart disease at baseline or by controlling for additional cardiovascular risk factors.16,18 The overall risk estimates provided by APCSC, PSC, and previous meta-analyses2,15,17 (a 5 mm Hg lower DBP or 10 mm Hg lower SBP was associated with approximately a 30% to 40% lower risk of stroke) were influenced by the mean age of the cohorts, as the association of BP with stroke varied with age. The proportional change in stroke risk per unit change in BP was less extreme in old age than in middle age (Figure 1), but the relationship remained strong and positive for all age groups.16,18 Age attenuation limits the ability to directly compare the summary relative risk estimates across the overviews, but the 2 recent overviews that have published age-specific relative risks had similar results (Table 1)16,18: a 10 mm Hg lower SBP was associated with approximately a 40% to 50%, 30% to 40%, and 20% to 30% lower risk of stroke in those aged <60 years, 60 to 69 years, and ≈70 years, respectively. There has been no evidence in any of the overviews that the strength of association between BP and stroke varied by sex2,15,16,18 or for fatal and nonfatal stroke events.2,18 Regional comparisons in APCSC and PSC suggested that the association between BP and stroke in Asia was similar or even slightly steeper than in Australia and New Zealand,18 Europe,16 and the United States after standardization for age. In these 2 overviews the associations of BP with stroke subtypes were broadly similar,16,18 although low rates of CT/MRI confirmation would tend to obscure any differences.

### Randomized Controlled Trials

Randomized controlled trials provide data on the impact of BP lowering on short-term stroke outcomes, which is relevant in assessing the extent to which the epidemiologically expected reductions in stroke are produced.2,3

**Randomized Controlled Trials Comparing Antihypertensive Drugs With a Placebo (or No Treatment)**

Seventeen trials compared the effects of β-blocker and/or diuretic with a placebo or no treatment; in 6 trials the comparison drug was angiotensin-converting enzyme (ACE) inhibitors, and in 2 it was calcium antagonists (Table
In total, there were >73,500 participants and almost 2,900 stroke events recorded in these trials. Weighted mean follow-up time for the 3 groups of trials ranged from 2.8 to 4.6 years, and the weighted mean age of participants ranged from 57 to 68 years. There was clear evidence of a reduction in stroke risk with BP lowering with each drug versus placebo comparison ($P < 0.005$), with pooled relative risk reductions for β-blocker and/or diuretic, ACE inhibitors, and calcium antagonists of 35%, 28%, and 39%, respectively. These broadly similar relative risk reductions were achieved with weighted mean reductions in BP (SBP/DBP) of 13/6, 5/2, and 10/5 mm Hg, respectively. While the BP reductions appeared less for the ACE inhibitor versus placebo trials, there is also greater uncertainty over the BP reductions in this subgroup.²⁹ There was no evidence of small study bias²⁰ as assessed by a funnel plot¹⁴ (not shown) and no significant statistical heterogeneity in any of the 3 subgroup comparisons.

<table>
<thead>
<tr>
<th>TABLE 2. Randomized Controlled Trials Comparing Antihypertensive Drugs to a Placebo (or No Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Beta-blocker and/or diuretic vs placebo or no treatment</td>
</tr>
<tr>
<td>ANBPS⁵⁰</td>
</tr>
<tr>
<td>Barraclough⁵¹‡§</td>
</tr>
<tr>
<td>Carter et al⁵²</td>
</tr>
<tr>
<td>Coope⁵³</td>
</tr>
<tr>
<td>Dutch TIA⁴⁴</td>
</tr>
<tr>
<td>EWPHE⁵⁵</td>
</tr>
<tr>
<td>HDFp⁵⁶–⁶⁰</td>
</tr>
<tr>
<td>HSICG I II III¹²⁵</td>
</tr>
<tr>
<td>MRC older⁶²</td>
</tr>
<tr>
<td>MRC young⁶³</td>
</tr>
<tr>
<td>Oslo⁴⁴⁵⁶</td>
</tr>
<tr>
<td>SHEP⁶⁶‡</td>
</tr>
<tr>
<td>STOP H⁶⁷</td>
</tr>
<tr>
<td>USPHS⁶⁸‡</td>
</tr>
<tr>
<td>VA⁶⁹–⁷⁰‡</td>
</tr>
<tr>
<td>VA-NHLBI⁷¹,⁷²</td>
</tr>
<tr>
<td>Wolff et al⁷³</td>
</tr>
<tr>
<td>Summary†</td>
</tr>
<tr>
<td>ACE inhibitors vs placebo</td>
</tr>
<tr>
<td>HOPE⁷⁴</td>
</tr>
<tr>
<td>PART ²⁷</td>
</tr>
<tr>
<td>PROGRESS²⁷</td>
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<tr>
<td>QUIET²⁸</td>
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<td>SCAT²⁷</td>
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<tr>
<td>TEST²⁸</td>
</tr>
<tr>
<td>Summary†</td>
</tr>
<tr>
<td>Calcium antagonists vs placebo</td>
</tr>
<tr>
<td>PREVENT⁷⁹</td>
</tr>
<tr>
<td>Syst-Eur⁴⁷</td>
</tr>
<tr>
<td>Summary†</td>
</tr>
</tbody>
</table>

n = number of events; N = number of participants. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; RR, relative risk; 95% CI, 95% confidence interval; NR, not recorded.

*Net BP difference = blood pressure difference between the randomized groups in mm Hg (ie, BP change in treatment group − BP change in placebo group).

†Summary follow-up, mean age, % male, and net SBP and DBP change are weighted by study size for those studies that provided data on net changes in both SBP and DBP. Weighting by number of events made negligible difference. The pooled RR and 95% CI (using the fixed effects approach) for each of the 3 trial subgroups are presented, and the test for heterogeneity (Q statistic and P value) are Q = 14.23, P = 0.36; Q = 8.90, P = 0.11; and Q = 0.61, P = 0.43, respectively.

‡ These trials also included older classes of drugs such as methyldopa and alkaloids.

§ There were no stroke events in the Barraclough or VA-NHLBI trial; however, for the purposes of meta-analyses, 0.5 was added to all cells in the 2 × 2 table.
Table 3. Randomized Controlled Trials Comparing Different Antihypertensive Drugs

Fifteen trials compared the effects of different types of antihypertensive drugs, with 2 trials including several drug versus drug comparisons (Table 4).22–24,46,80–92 In total, there were >96 000 participants and almost 3600 stroke events recorded over a mean follow-up time of 4 to 5 years. The weighted mean reduction in BP in many of the drug versus drug trials was small, often <1 mm Hg SBP and DBP (Table 4). Overall, these trials indicated that there was little difference between the drug classes, with relative risk reductions of 9% (β-blockers and/or diuretics versus ACE inhibitors), 8% (β-blockers and/or diuretics versus calcium antagonists), and 11% (calcium antagonists versus ACE inhibitors). These results were of borderline statistical significance. The latter subgroup was the only one in which there was evidence of statistical heterogeneity (P=0.09), and a random effects model gave a nonsignificant relative risk reduction of 5%.

Net Reduction in BP and Relative Risk Reduction in Stroke

A meta-regression analysis was used to assess the direct relationship between the net reduction in SBP in the 7 trial meta-analyses. The net reduction in SBP was plotted against the relative risk reduction in stroke for each meta-analysis. This plot suggested that a dose-response relationship may exist (Figure 3). A weighted linear regression line was superimposed in which weights are equal to the inverse of the variance for each trial meta-analysis. The slope of this weighted regression line indicated that a 10 mm Hg greater reduction in SBP would be associated with a reduction in risk of stroke of 31% ($R^2=0.71$). The mean weighted follow-up duration for all these trials was 4.5 years, and the mean weighted age of participants at entry into trials was 63 years (the mean age at event is likely to be approximately a decade later). Age-specific analyses from the 2 cohort study overviews16,18 estimated that a 10 mm Hg lower SBP in participants aged 60 to 69 years at event was associated with a risk reduction in stroke of approximately 35%; for those aged ≥70 years the risk reduction was 25% to 29% (Table 5). The results from cohort studies and randomized controlled trials are therefore broadly consistent, suggesting that most of the “epidemiologically expected” benefit of BP lowering is achieved within a few years for stroke.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Net difference</th>
<th>Relative risk reduction of stroke (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 years</td>
<td>12 / 4</td>
<td>46% (26–57%)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>6 / 3</td>
<td>28% (23–35%)</td>
</tr>
<tr>
<td>70+ years</td>
<td>11 / 6</td>
<td>28% (21–35%)</td>
</tr>
<tr>
<td>Mean baseline SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 160 mmHg</td>
<td>3 / 1</td>
<td>30% (15–45%)</td>
</tr>
<tr>
<td>&gt; 160–179 mmHg</td>
<td>14 / 4</td>
<td>26% (17–53%)</td>
</tr>
<tr>
<td>&gt; 179 mmHg</td>
<td>15 / 6</td>
<td>32% (25–38%)</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few/no participants</td>
<td>11 / 5</td>
<td>30% (24–41%)</td>
</tr>
<tr>
<td>Most/all participants</td>
<td>9 / 4</td>
<td>22% (12–35%)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few/no participants</td>
<td>13 / 6</td>
<td>34% (29–49%)</td>
</tr>
<tr>
<td>Most/all participants</td>
<td>6 / 3</td>
<td>24% (16–31%)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>30% (24–32%)</td>
</tr>
</tbody>
</table>

Figure 2. Randomized controlled trials comparing antihypertensive drugs with a placebo (or no treatment) by subgroup. The meta-analyses of BP-lowering trials are presented stratified into subgroups on the basis of mean age of trial participants at entry, baseline SBP level, and whether trial participants predominantly had a history of stroke/transient ischemic attack (TIA) or vascular disease. The diamonds are centered on the pooled estimate of effect and represent 95% CI. The solid diamond represents the pooled relative risk and 95% CI for all contributing trials.

The trials comparing antihypertensive drugs with a placebo (or no treatment) were stratified by several trial characteristics such as mean age at entry, baseline BP, and history of cardiovascular disease (Figure 2). Overall, there was a reduction in risk of stroke of 30% and a risk reduction of approximately 30% to 40% in most subgroups. However, in several groups the risk reduction appeared to be greater with larger net reduction in BP, for example, in those with no past history of stroke/transient ischemic attack or vascular disease.

Randomized Controlled Trials Comparing More Intensive Versus Less Intensive Antihypertensive Drug Regimens

Three individually inconclusive clinical trials including a total of 20 408 participants and 384 stroke events compared treatment regimens of different intensities21–24 (Table 3). The meta-analysis suggested that additional benefit may be gained from a more intensive treatment regimen (relative risk reduction of 20%; $P=0.04$). There was no significant statistical heterogeneity.

<table>
<thead>
<tr>
<th>More Intensive vs Less Intensive Trials</th>
<th>More</th>
<th>Less</th>
<th>Follow-Up,</th>
<th>Mean Age,</th>
<th>% Male</th>
<th>Net Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>N</td>
<td>n</td>
<td>N</td>
<td>y</td>
<td>y</td>
<td>%</td>
</tr>
<tr>
<td>ABCD22</td>
<td>9</td>
<td>237</td>
<td>9</td>
<td>233</td>
<td>5.3</td>
<td>58</td>
</tr>
<tr>
<td>HOT 23</td>
<td>89</td>
<td>6262</td>
<td>205</td>
<td>12528</td>
<td>3.8</td>
<td>62</td>
</tr>
<tr>
<td>UKPDS-HDS 23,24</td>
<td>38</td>
<td>758</td>
<td>34</td>
<td>390</td>
<td>8.4</td>
<td>56</td>
</tr>
<tr>
<td>Summary†</td>
<td>136</td>
<td>7257</td>
<td>248</td>
<td>13 151</td>
<td>4.2</td>
<td>62</td>
</tr>
</tbody>
</table>

n = no. of events, N = no. of participants. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; RR, relative risk; 95% CI, 95% confidence interval.

* Net BP difference = blood pressure difference between the randomized groups (mm Hg) (ie, BP change in more intensive drug treatment group – BP change in less intensive drug treatment group).

†Summary follow-up, mean age, % male, and net SBP and DBP change are weighted by study size for those studies that provided data on net changes in both SBP and DBP. Weighting by number of events made negligible difference. The pooled RR and 95% confidence interval (using the fixed effects approach) are presented, and the test for heterogeneity (Q statistic and $P$ value) are $Q=2.70$, $P=0.26$. 

TABLE 3. Randomized Controlled Trials Comparing More Intensive vs Less Intensive Antihypertensive Drug Regimens
Calcium antagonists vs ACE inhibitors

Because most of the cohort studies have been conducted primarily in the "developed" parts of the world, it is likely that the higher overall stroke rate in this group means that in absolute terms, the benefits of a given reduction in BP are potentially weaker relative association for older age groups, compared with proportionately younger populations. Previous meta-analyses and confirmed the risk reduction of stroke with BP lowering compared with placebo (regardless of the agent used) as being between 30% and 40%. Despite a potentially weaker relative association for older age groups, the higher overall stroke rate in this group means that in absolute terms, the benefits of a given reduction in BP are likely to be greater. The analyses have not consistently demonstrated a difference in the association between intracerebral hemorrhage and ischemic stroke; however, only approximately one half of stroke subtypes were confirmed (CT, MRI, or autopsy). Regional comparisons are very limited because most of the cohort studies have been conducted primarily in the "developed" parts of the world, however, the broad consistency of the results across overviews was more evident than any differences. This suggests that the proportional associations are likely to be reasonably generalizable to the many populations in the world (eg, Africa, South America) for which there are limited data on stroke epidemiology.25

**Summary**

Data from trials provide more reliable data on the likely short-term benefits of BP lowering on stroke. As with the cohort data, randomized controlled trials have been conducted predominantly in populations of Western countries, and data for developing countries (where approximately three quarters of stroke deaths occur worldwide26) are very scarce. The results of the updated meta-analysis of trials are consistent with those of previous meta-analyses and confirmed the risk reduction of stroke with BP lowering compared with placebo (regardless of the agent used) as being between 30% and 40%. Previous analyses have also found no evidence of a difference in effect.

**TABLE 4. Randomized Controlled Trials Comparing Different Blood Pressure–Lowering Drugs**

<table>
<thead>
<tr>
<th>Drug vs Drug Trials</th>
<th>First Drug</th>
<th>Second Drug</th>
<th>Follow-Up, y</th>
<th>Mean Age, y</th>
<th>% Male</th>
<th>SBP</th>
<th>DBP</th>
<th>RR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers and/or diuretics vs ACE inhibitors</td>
<td>ALLHAT80</td>
<td>675</td>
<td>15255</td>
<td>457</td>
<td>9045</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>ANBPS81</td>
<td>107</td>
<td>3039</td>
<td>112</td>
<td>3044</td>
<td>4.1</td>
<td>72</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>CAPPPP82</td>
<td>148</td>
<td>5493</td>
<td>189</td>
<td>5492</td>
<td>6.1</td>
<td>53</td>
<td>53</td>
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<tr>
<td></td>
<td>STOP-246</td>
<td>237</td>
<td>2213</td>
<td>215</td>
<td>2205</td>
<td>5.0</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>UKPDS-HDS 23,24</td>
<td>17</td>
<td>358</td>
<td>21</td>
<td>400</td>
<td>8.4</td>
<td>56</td>
<td>54</td>
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<tr>
<td></td>
<td>Summary†</td>
<td>1184</td>
<td>26358</td>
<td>994</td>
<td>20195</td>
<td>5.1</td>
<td>65</td>
<td>51</td>
</tr>
<tr>
<td>Beta-blockers and/or diuretics vs calcium antagonists</td>
<td>ALLHAT80</td>
<td>675</td>
<td>15255</td>
<td>377</td>
<td>9048</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>CASTEL83</td>
<td>5</td>
<td>205</td>
<td>5</td>
<td>146</td>
<td>7.0</td>
<td>73</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>CONVINCE84</td>
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<td>133</td>
<td>8179</td>
<td>3.0</td>
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<td>44</td>
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<tr>
<td></td>
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<td>14</td>
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<td>9</td>
<td>1177</td>
<td>4.0</td>
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<td>55</td>
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<td>INSIGHT86</td>
<td>74</td>
<td>3164</td>
<td>67</td>
<td>3157</td>
<td>4.0</td>
<td>65</td>
<td>46</td>
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<tr>
<td></td>
<td>MIDAS97</td>
<td>3</td>
<td>441</td>
<td>6</td>
<td>442</td>
<td>3.0</td>
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<td>78</td>
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<tr>
<td></td>
<td>NICS-EH98</td>
<td>8</td>
<td>214</td>
<td>6</td>
<td>215</td>
<td>5.0</td>
<td>70</td>
<td>33</td>
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<tr>
<td></td>
<td>NORDIL99</td>
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<td>5471</td>
<td>159</td>
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<td>5.0</td>
<td>60</td>
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<tr>
<td></td>
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<td>237</td>
<td>2213</td>
<td>207</td>
<td>2196</td>
<td>5.0</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>UKPDS-HDS 23,24</td>
<td>4</td>
<td>707</td>
<td>5</td>
<td>707</td>
<td>2.0</td>
<td>54</td>
<td>49</td>
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<tr>
<td></td>
<td>Summary†</td>
<td>1334</td>
<td>37124</td>
<td>974</td>
<td>30677</td>
<td>4.2</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>Calcium antagonists vs ACE inhibitors</td>
<td>ABCD27</td>
<td>11</td>
<td>235</td>
<td>7</td>
<td>235</td>
<td>5.3</td>
<td>58</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>ALLHAT80</td>
<td>377</td>
<td>9048</td>
<td>457</td>
<td>9054</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
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<tr>
<td></td>
<td>FACET28</td>
<td>10</td>
<td>191</td>
<td>4</td>
<td>189</td>
<td>3.5</td>
<td>63</td>
<td>41</td>
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<tr>
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<td>STOP-246</td>
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<td>2196</td>
<td>215</td>
<td>2205</td>
<td>5.0</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Summary†</td>
<td>605</td>
<td>11670</td>
<td>683</td>
<td>11683</td>
<td>4.9</td>
<td>68</td>
<td>49</td>
</tr>
</tbody>
</table>

n = no. of events, N = no. of participants; SBP indicates systolic blood pressure; DBP, diastolic blood pressure; RR, relative risk; 95% CI, 95% confidence interval.

*Net BP difference = blood pressure difference between the randomized groups (mm Hg). Presented as the BP change in (first listed drug)–(second listed drug), ie, a negative value means that the second listed drug achieved a greater blood pressure reduction than the first listed drug.

†Summary follow-up, mean age, % male, and net SBP and DBP change are weighted by study size for those studies that provided data on net changes in both SBP and DBP. Weighting by number of events made negligible difference. The pooled RR and 95% confidence interval (using the fixed effects approach) for each of the 3 trial subgroups are presented, and the test for heterogeneity (Q statistic and P value) are Q = 6.91, P = 0.14; Q = 7.36, P = 0.59; and Q = 6.53, P = 0.09, respectively. The pooled RR and 95% CI using a random effects approach for the last trial subgroup was 0.95 (0.76–1.19).

**Discussion**

Cohort studies have demonstrated that the strong association between BP and stroke appears to be continuous down to levels of at least 115/75 mm Hg. The strength of the associations was similar for men and women and for fatal and nonfatal events but attenuated with age.2,13–18 Despite a potentially weaker relative association for older age groups, the higher overall stroke rate in this group means that in absolute terms, the benefits of a given reduction in BP are likely to be greater. The analyses have not consistently demonstrated a difference in the association between intracerebral hemorrhage and ischemic stroke; however, only approximately one half of stroke subtypes were confirmed (CT, MRI, or autopsy). Regional comparisons are very limited because most of the cohort studies have been conducted primarily in the “developed” parts of the world; however, the
size for men and women or for fatal and nonfatal events.\textsuperscript{3–8} Limited data were available on treatment effects by age, and the treatment effects by age within individual trials\textsuperscript{27} and between trials\textsuperscript{4,5,9,10,28} have not been consistent. However, the trials were often not powered for age subgroup analyses and often included only a narrow age band. Few data are available on stroke subtypes, limiting the scope for meta-analyses. The limited data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)\textsuperscript{27} and the Heart Outcomes Prevention Evaluation (HOPE) study\textsuperscript{29} are insufficient to draw definitive conclusions regarding the impact of BP lowering on stroke subtypes. Analysis\textsuperscript{es} have indicated, however, that a more intensive BP-lowering regimen with a given agent may produce a greater risk reduction than a less intensive regimen and that overall the trials demonstrate a dose-response relationship between magnitude of BP reduction and reduction in risk of stroke.

When different classes of BP-lowering drugs were directly compared, there was very little difference in either the magnitude of the BP reduction achieved or the impact of different agents on stroke. The similarities between the effects of different drug classes are more striking than the differences, but there is uncertainty over the extent to which any differences are explained by differences in BP reduction and chance. One arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)\textsuperscript{30} and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE)\textsuperscript{31,32} were not included in the meta-analysis because no other trials included the same classes of drugs. They indicated that there was a higher risk of stroke in the \(\alpha\)-adrenergic blocker group compared with diuretics\textsuperscript{30} and that angiotensin II blockers may have greater impact on stroke than \(\beta\)-blockers.\textsuperscript{31,32}

**Shape and Size of Association Between BP and Stroke**

There has been considerable debate over the shape of the association between BP and stroke. The data presented here from cohort studies suggested a continuous log-linear association. However, some other cohort data appear to have demonstrated a J-shaped curve.\textsuperscript{33–37} It has been suggested that this relationship indicates that BP has been lowered too far and that cerebral blood flow is compromised, leading to ischemia. It is more likely to reflect deteriorating health, which accounts for both falling pressure and a greater likelihood of a cardiovascular disease event, but the 2 factors may not be causally related.\textsuperscript{38–43} Several trials have found no evidence of a J-curve association despite including subgroups of patients susceptible to reduced perfusion.\textsuperscript{44–47} The large PROGRESS\textsuperscript{48} and HOPE\textsuperscript{29} trials found no evidence of a J-curve association across a wide range of BP levels. Overall, these results support a log-linear association and indicate that a potential J-curve relationship should not detract attention from the major benefits of BP lowering.

A key finding from this article is that the 7 meta-analyses of randomized controlled trials of BP lowering and stroke

![Figure 3](image-url)

**Figure 3.** Net reduction in SBP and relative risk reduction in stroke in randomized controlled trials of BP lowering. In a meta-regression, the direct relationship between the net reduction in SBP was plotted against the relative risk reduction in stroke for each of the 7 trial meta-analyses. The slope of the weighted linear regression line (where weights are equal to the inverse of the variance for each trial meta-analysis) indicated that a 10 mm Hg greater reduction in SBP would be associated with a reduction in risk of stroke of 31% \((R^2=0.71)\). From left to right, the diamonds represent the meta-analyses for \(\beta\)-blockers and/or diuretics vs ACE inhibitors, and \(\beta\)-blockers and/or diuretics vs ACE inhibitors; the circle represents the more intensive vs less intensive antihypertensive drug regimens; and the squares are ACE inhibitors; and \(\beta\)-blockers and/or diuretics vs placebo or no treatment. The size of the diamonds, circle, and squares are larger where there are more events because their size is proportional to the inverse variance of that comparison; vertical lines represent 95% CI.

---

**TABLE 5. Relative Risk Reduction in Stroke With a Reduction in Systolic Blood Pressure Predicted From Cohort Studies and Observed From Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>Predicted Effects on Stroke of Lowering SBP 10 mm Hg*</th>
<th>Mean Age at Event</th>
<th>Estimated Mean Age at Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60–69 Years</td>
<td>70–79 Years</td>
</tr>
<tr>
<td>Prospectives Studies Collaboration (2002)\textsuperscript{16}</td>
<td>34%</td>
<td>29%</td>
</tr>
<tr>
<td>Asia Pacific Cohort Studies Collaboration (2003)\textsuperscript{18}</td>
<td>36%</td>
<td>25%</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure.

*Relative risk reduction in stroke from cohort studies with a 10-mm Hg lower SBP, by age at event.

†Relative risk reduction in stroke from randomized controlled trials with a 10-mm Hg reduction in SBP based on the slope of the regression line in Figure 3. Mean age at entry into trials was 63 years, and mean age at event is likely to approximately a decade later, ie, 73 years.
suggest a dose-response relationship. At mean age at baseline of approximately 63 years, a 10 mm Hg reduction in SBP was associated with a risk reduction in stroke of 31%. Given that most of these individuals would not have experienced their stroke event until approximately a decade later, the results are consistent with the predicted reduction in stroke risk from the cohort study data. This indicates that most of the epidemiologically expected benefit of BP lowering may be achieved within a few years for stroke.

Future Research and Implications for Prevention

Research and analyses from cohort study collaborations such as APCSC and meta-analysis of individual participant trial data improve the understanding of the associations between BP and stroke and the potential benefits of BP lowering in different population subgroups. Additional analyses are able to examine the combined impact of multiple risk factors on stroke risk. BP intervention strategies would be greatly enhanced if these data were also used in the improvement of risk prediction frameworks to better identify those at higher absolute risk of cardiovascular disease. Development of simple versions of these risk prediction tools would be of particular value in developing regions where much of the future cardiovascular disease burden is likely to occur.1,49

Future trial analyses should focus on the presence or absence of age attenuation in the effect of BP lowering. This would require comparison of age-specific, follow-up time-specific, and end point-specific analyses of individual participant data from both observational studies (such as APCSC) and clinical trials (such as the Blood Pressure Lowering Treatment Trialists’ Collaboration111). Given that most individuals require combination therapy, it is also important to shift the focus of trials from comparisons of the short-term benefits of individual drugs. Instead, future trials should aim to determine the optimal combination therapy and the potential long-term benefits of different antihypertensive regimens in different population subgroups. While there may be some differences between BP-lowering agents, the relative differences between these agents are minor compared with the relative benefits of any BP-lowering agent versus no treatment.

Finally, it is important to acknowledge that treatment of high-risk groups will only partially address the growing cardiovascular disease epidemic. Data presented in this article indicated that the relative benefits of BP lowering are not only limited to those classified as hypertensive but would also be evident in those with normal or below normal BP. These relative benefits appear broadly consistent across many population subgroups. Other important areas of research therefore include exploration of cost-effective strategies to bring about population changes in cardiovascular risk factors such as BP. Such initiatives would complement targeted treatment approaches and would not only benefit the developed world but could potentially arrest the projected increase in cardiovascular disease in developing countries.

Acknowledgments

This study was supported by a Health Research Council (New Zealand) fellowship to Dr Lawes. Dr Rodgers is a National Health Foundation (New Zealand) Senior Research Fellow. We thank Varsha Parag and Ruey-Bin Lin for statistical assistance and Clarissa Could-Thorpe for secretarial support.

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